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DOI: 10.17235/reed.2019.6594/2019
Link: PubMed (Epub ahead of print)

Please cite this article as:

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EDITORIAL 6594 inglés

Shadows in the current management of hepatocellular carcinoma in Spain - An embarrassing truth

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Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related deaths worldwide (1). Up to 80% of patients with HCC have concomitant cirrhosis as a result of hepatitis B or C virus, alcohol abuse, or non-alcoholic steatohepatitis (2). Unfortunately, only up to 40% of patients with HCC are diagnosed in early stages, when therapies are available with curative intent. Therefore, many patients, likely around 50%, must receive systemic treatment for HCC over the course of this neoplasm (3,4). Since approval back in 2007, sorafenib has remained the only systemic therapy that has proven effective against HCC, with repeatedly positive results (5). Over the past two years efficacy has been established for lenvatinib (first-line) and regorafenib, cabozantinib and ramucirumab (second-line), which means that patients with advanced disease have a modest but consistent increase in life expectancy (6-11). These results have led both regulatory agencies and scientific societies to authorize and/or recommend the use of these antineoplastic drugs. As may be seen in table 1, there is unanimity amongst regulatory agencies regarding the approval of first-line sorafenib and lenvatinib, and second-line regorafenib and cabozantinib (12-24).
Probably because results were reported very recently, only the FDA has yet approved the use of ramucirumab in the second line of treatment. Position statement documents and guidelines by scientific societies are conclusive: in all cases is the use of first-line sorafenib and lenvatinib supported, as is the use of second-line regorafenib, cabozantinib and ramucirumab, provided the relevant information was already available at the time of guideline publication (25-30). Lastly, the British agency NICE, whose reports, far removed from any unscientific bias, are completely trustworthy because of their stringency, has also issued a positive report for regorafenib and lenvatinib, while the other drugs remain to be assessed (31,32). It is after observing this unanimity among regulatory agencies and guidelines by scientific societies that our first unpleasant surprise occurs: in Spain funding is only available for sorafenib.

This fact has double motivation: a) a surprising decision by the Ministry of Health to approve the indication but not the funding of regorafenib; and b) the amazing sluggishness of our therapeutic positioning reports (TPRs), with those related to lenvatinib and cabozantinib still pending publication. The second, also unpleasant surprise, namely the inequity extant in our health services, is particularly disturbing. While in some Communities (or even hospitals) our patients with hepatocellular carcinoma may receive second-line regorafenib, in others, actually in most of them, our health authorities deny access to this drug based on its lack of funding despite an approved indication. This inequity situation is even worse when considering that access to lenvatinib and cabozantinib is for compassionate use, its authorization being left at the discretion of each center. That is, while some patients with HCC may benefit from the complete therapeutic armamentarium presently available, others can only have access to sorafenib, even though there is more than enough evidence supporting the use of other drugs when sorafenib fails to be effective or loses efficacy after a period of time in use.

In the second part of this editorial we must denounce the present situation of HCC management in the Basque Country. Recently, Osakidetza (the Basque Health Service) presented the Basque Country’s Oncologic Plan, and immediately afterwards Osakidetza’s Territorial Assistance Office ordered their tertiary hospital boards to process all cancer drug prescriptions through Onkobide, an application to which
gastroenterology and hepatology specialists will have no access (33). At both the Spanish Association for the Study of the Liver (AEEH) and the Spanish Society of Digestive Diseases (SEPD) we radically reject such measure. Our rejection is based on the following reasons:

– Cancer management cannot be thought of in isolation. Any approach to cancer must include epidemiology; primary, secondary and tertiary prevention; natural history of the disease; potential complications; diagnosis, prognosis, and treatment. Explicitly, cancer management is not restricted to the administration of different drugs in certain stages of tumor progression.

– Regarding HCC, this tumor develops in patients with liver cirrhosis in over 90% of cases. Because of this peculiarity, the vast majority of patients with HCC develop complications arising not from the tumor itself but from liver cirrhosis. Gastroenterologists and hepatologists (G&H) are the specialists best qualified for the appropriate management of these complications (34).

– The development of systemic therapy for HCC has been led by Spanish hepatologists. Because of this relevant fact, our G&H are familiar with systemic HCC therapy from the very start. In fact, our specialists are considered as experts in the treatment of HCC on an international basis. Therefore, we are also obviously qualified for the management of the potential toxicities induced by the drugs currently approved for the treatment of HCC, and so shall we remain when it comes to handling the newer agents to be authorized in the upcoming future.

– Our legal system (Orden SAS/2854/2009, de 9 de octubre, por la que se aprueba y publica el programa formativo de la especialidad de Aparato Digestivo. Nº 258 de lunes 26 de octubre de 2009. Sec. III. Pág. 89582) establishes that: “...a digestive system specialist must have the necessary knowledge, skills, and attitudes to orient the clinical diagnosis of patients with digestive diseases [...] mostly control patients with serious conditions (liver cirrhosis, inflammatory bowel disease, digestive cancer)....”. Specifically and unequivocally, reference is made to the specialist’s competence in the diagnosis and treatment of HCC. Similarly, in our neighboring countries G&H are deemed to be competent in HCC diagnosis, staging, and management. In this regard, the European Blue Book for digestive system diseases
may be consulted (35).

- The split in patient care established by Osakidetza between prescribing physicians (oncologists) and physicians who treat complications for patients with HCC (gastroenterologists) is a profound error, a poorly efficient measure that will result in delayed care and gratuitous annoyance for patients with HCC.

- We believe that the diagnosis and treatment of patients with HCC should be multidisciplinary, with G&H at the hub of patient care because of their being the best qualified specialists in the holistic management of these individuals, understanding that the underlying disease (cirrhosis) and the emerged complication (HCC) cannot be divorced from each other.

We have no doubt whatsoever that we, G&H, are qualified to manage, in a multidisciplinary setting, our patients with cancer, and specifically our patients with HCC. We believe in the multidisciplinary approach to cancer, and we believe in our role in the management of multiple tumors including HCC, where our intervention is key. In addition to our competence and qualifications this plan disregards the law since our current training program supports our role in the holistic management of digestive cancer, with an emphasis on hepatocellular carcinoma.

As chairs of the AEEH, SEPD and Spanish National Commission on Digestive Diseases (CND) we believe that for our patients to benefit from the best treatment possible, administered by the best qualified professionals:

1. Our national health authority must approve funding for regorafenib within the shortest possible period of time, and press for TPR completion to allow the funding and use of lenvatinib and cabozantinib. Only in this way will the serious burden of inequity currently overwhelming patients with HCC in our country cease to exist.

2. G&H should lead the multidisciplinary teams responsible for the diagnosis, monitoring and treatment of patients with HCC. We ask of healthcare authorities to revoke this clearly wrong decision in order to allow patients to receive their treatments from their G&H, which should be obviously empowered to prescribe the most appropriate treatment available.

**ACKNOWLEDGEMENTS**
Dr. Andrade and Dr. Crespo wish to thank Dr. María Varela (Hospital Universitario Central de Asturias) and Dr. Carlos Rodríguez de Lope (Hospital Universitario Marqués de Valdecilla) for their scientific advice.

REFERENCES

18. U.S. Food and Drug Administration. FDA approves durvalumab after chemoradiation for unresectable stage III NSCLC. Disponible en: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm555548.htm


36. Acuerdos de la reunión de la Comisión Interministerial de precios de los
Table 1. Approval of first-line sorafenib and lenvatinib use and second-line regorafenib and cabozantinib use by regulatory agencies. Position statement documents and guidelines issued by scientific societies

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib</th>
<th>Lenvatinib</th>
<th>Regorafenib</th>
<th>Cabozantinib</th>
<th>Ramucirumab</th>
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<tbody>
<tr>
<td>Indication</td>
<td>1st line</td>
<td>1st line</td>
<td>2nd line after sorafenib in patients tolerant to sorafenib</td>
<td>2nd line after sorafenib</td>
<td>2nd line after sorafenib if AFP &gt; 400</td>
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<tr>
<td>AEMPS approval</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>EMA approval</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>AEEH position statement (2016)*</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>EASL position statement (2018)'</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Favorable report</td>
</tr>
<tr>
<td>AASLD position</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Statement</td>
<td>APASL position statement (2017)§</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
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<td>ESMO position statement (2018)ǁ</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>NCCN position statement (2019)¶</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Therapeutic positioning report (TPR)</td>
<td>Yes</td>
<td>Pending</td>
<td>Yes. Compensated patients with HCC, ECOG PS 0-1 and tolerant to prior sorafenib may be treated in 2nd line</td>
<td>Pending</td>
<td>Not assessed</td>
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<td>NHS funding</td>
<td>Yes</td>
<td>No, TPR pending</td>
<td>No, refused by the CIPM**</td>
<td>NO, TPR pending</td>
<td>No</td>
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<td>Available to Autonomous Communities (ACs)</td>
<td>Yes</td>
<td>Compassionate use. Depending on each AC and/or center</td>
<td>At the discretion of each AC</td>
<td>Compassionate use. Depending on each AC and/or center</td>
<td>No</td>
</tr>
</tbody>
</table>
*AEEH (2016): published in 2016. It includes recommendation for sorafenib. As regards the other drugs, no clinical trial results were then available showing improved survival (or non-inferiority). †EASL (2018): published in 2018. The ramucirumab trial was not finished yet at the time of publication. ‡AASLD (2018): the August 2018 update includes 1st-line sorafenib and lenvatinib, and 2nd-line regorafenib and cabozantinib. The ramucirumab trial was pending publication at the time. §APASL (2017): it includes sorafenib (1st-line) and regorafenib (2nd-line). Results pending at the time of publication for the other drugs. ¶ESMO (2018): it includes 1st-line sorafenib and lenvatinib. 2nd-line regorafenib, cabozantinib and ramucirumab. †NCCN (2019): it also includes 1st-line sorafenib and lenvatinib and 2nd-line regorafenib, cabozantinib and ramucirumab (these guidelines also include other options with lower evidence levels). **CIPM: Comisión Interministerial de Precios de Medicamentos y productos sanitarios (36).